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The sex-shift in single disease and multimorbid asthma and rhinitis during puberty - a study by MeDALL

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Abstract

Background: Cross-sectional studies suggested that allergy prevalence in childhood is higher in boys compared to girls, but it remains unclear whether this inequality changes after puberty. We examined the sex-specific prevalence of asthma and rhinitis as single and as multimorbid diseases before and after puberty onset in longitudinal cohort data.

T. Keil and S. Roll contributed equally.

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Methods: In six European population-based birth cohorts of MeDALL, we assessed the outcomes: current rhinitis, current asthma, current allergic multimorbidity (ie, concurrent asthma and rhinitis), puberty status and allergic sensitization by specific serum antibodies (immunoglobulin E) against aero-allergens. With generalized estimating equations, we analysed the effects of sex, age, puberty (yes/no) and possible confounders on the prevalence of asthma and rhinitis, and allergic multimorbidity in each cohort separately and performed individual participant data meta-analysis.

Findings: We included data from 19 013 participants from birth to age 14-20 years. Current rhinitis only affected girls less often than boys before and after puberty onset: adjusted odds ratio for females vs males 0.79 (95%-confidence interval 0.73-0.86) and 0.86 (0.79-0.94), respectively (sex-puberty interaction $P = .089$). Similarly, for current asthma only, females were less often affected than boys both before and after puberty onset: 0.71, 0.63-0.81 and 0.81, 0.64-1.02, respectively (sex-puberty interaction $P = .327$). The prevalence of allergic multimorbidity showed the strongest sex effect before puberty onset (female-male-OR 0.55, 0.46-0.64) and a considerable shift towards a sex-balanced prevalence after puberty onset (0.89, 0.74-1.04); sex-puberty interaction: $P < .001$.

Interpretation: The male predominance in prevalence before puberty and the "sex-shift" towards females after puberty onset were strongest in multimorbid patients who had asthma and rhinitis concurrently.

KEYWORDS

allergic multimorbidity, asthma, birth cohort, puberty, rhinitis

1 | INTRODUCTION

The prevalence of two of the most common chronic diseases globally, asthma and rhinitis, remains at a high level or is still increasing in some parts of the world.[1-3] At around puberty, considerable sex-specific differences in the prevalence of allergic diseases have been identified.[4-6] For asthma, the prevalence is higher in boys than in girls before puberty, but after puberty, there is a female predominance persisting in adulthood.[7-10]

In rhinitis, sex-specific prevalence differences before and after puberty onset are less clear.[11] A recent meta-analysis of cross-sectional population-based studies suggested a "sex-switch" around puberty from male to female predominance in rhinitis prevalence.[12] However, longitudinal sex-specific evaluations from early childhood to adolescence regarding rhinitis as well as asthma prevalence are lacking. Long-term birth cohort studies are essential to understanding the life course and childhood predictors of allergies including sex-specific differences.[13] As the statistical power of individual cohorts is often insufficient to allow stratified analyses,[14] the European Commission funded MeDALL (Mechanisms of the Development of ALLergy; EU FP7-CP-IP; Project No: 261357; 2010-2015) with the aim to integrate 14 European birth cohorts including 44 010 participants for combined and harmonized analyses.[15]

This large data set allowed examining a potential sex-shift in the prevalence of less common but more severe allergic phenotypes such as multimorbidity of asthma and rhinitis and their association with and without allergen-specific immunoglobulin E (IgE) antibodies with the sufficient statistical power.[15]

Asthma and rhinitis are both heterogeneous diseases with many forms and phenotypes of different aetiologies; thus, we differentiated between asthma only and rhinitis only as single entities and multimorbidity.[15,16]

In the present analyses, we aimed to examine and compare a possible "sex-shift" in prevalence of asthma, rhinitis and multimorbidity (asthma and concurrent rhinitis) during puberty using the pooled MeDALL cohort data.

2 | METHODS

2.1 | Study design, setting and included birth cohorts

This study is based on the six older population-based birth cohorts from the MeDALL project.[15,17] We chose the following inclusion criteria: (i) at least one prospective assessment of asthma and rhinitis before puberty (ie, from birth to 10 years of age) and after possible puberty onset (11-18 years); (ii) at least one assessment of allergic sensitization based on specific antibodies against aero-allergens in serum; (iii) at least one prospective assessment of the puberty status at 10 years or older. The included birth cohorts were PIAMA (The Netherlands), BAMSE (Sweden), DARC (Denmark) and MAS, GINIplus and LISAplus (all Germany). All participating birth cohorts had obtained ethical approval from their local review boards. Recruitment, study design and data collection for the birth cohort studies have been described in detail previously.[18-22]

Information on health outcomes and puberty status has been collected at several time points. The number of time points and exact ages of the participants at follow-up differed between cohorts. When combining the cohorts, we had data for a total of 14 possible follow-up time points (Table S1).

A panel of experts within the MeDALL consortium followed a stringent process[23] for data harmonization between the participating cohorts. For each variable to be harmonized, a reference definition was agreed and each cohort then evaluated how their own cohort definition matched the reference definition as complete, partial or impossible. All single evaluations were then reviewed in a joint workshop to create the final harmonized data set.

2.2 | Outcome variables

2.2.1 | Primary outcomes

We defined three primary outcome measures: current asthma only, current rhinitis only and current allergic multimorbidity.

Current asthma only

"Current asthma only" was defined as a positive answer to at least two of the three following questions:

- "Has your child *ever* been diagnosed by a doctor as having asthma?"
- "Has your child (/Have you) taken any medication for asthma (including inhalers, nebulizers, tablets or liquid medicines) or breathing difficulties (chest tightness, shortness of breath) in the last 12 months?"
- "Has your child (/Have you) had wheezing or whistling in your chest at any time in the last 12 months?"[24]

and a negative "current rhinitis" status. If two of these three questions were answered with "no" at the respective follow-up, asthma status was negative.

Current rhinitis only

The occurrence of "current rhinitis only" at the respective follow-up assessment was defined by a positive (parent or self-reported) answer to the question "Has your child had/Did you have problems with sneezing, or a runny, or blocked nose when s/he/you did not have a cold or flu in the past 12 months?" (yes/no) based on the International Study of Asthma and Allergy in Childhood (ISAAC)[24] and a negative current asthma status. A negative answer to the question above defined a negative current rhinitis status.

Current allergic multimorbidity

A positive "current allergic multimorbidity" status was defined as concurrent asthma and rhinitis. If either rhinitis or asthma was negative, allergic multimorbidity status was defined as negative.

2.2.2 | Secondary outcomes

To investigate possible effects of puberty status on allergic sensitization, we included the following six secondary outcomes:

- "IgE-associated current rhinitis"
- "Non-IgE associated current rhinitis"
- "IgE-associated current asthma"
- "Non-IgE associated current asthma"
- "IgE-associated current allergic multimorbidity (asthma and rhinitis)"
- "Non-IgE associated current allergic multimorbidity (asthma and rhinitis)".

A positive allergic sensitization status was defined as specific immunoglobulin E (IgE) $\geq$ 0.35 kU/L in serum against at least one common aero-allergen (dog, cat, house dust mite or birch pollen, as they were assessed in all included cohorts) at the same follow-up at which the clinical phenotypes were assessed or, if serum samples were missing, at the preceding follow-up. A negative allergic sensitization status was defined as s-IgE < 0.35 kU/L against all four common aero-allergens.

As a sensitivity analysis, we defined the six secondary outcomes including sensitization status based on IgE against food and aero-allergens, defined as s-IgE $\geq$ 0 .35 kU/L against at least one common food (cow's milk, hen's egg, peanut) or aero-allergen. A negative allergic sensitization status was defined as s-IgE < 0.35 kU/L against all of the seven allergens.

2.3 | Definition of main exposure variable puberty

Puberty categories were defined using the Puberty Development Scales (PDS).[25,26] For boys, the following items were included: (i) body hair growth, (ii) voice change and (iii) facial hair growth. For girls, the Puberty Category Scores (PCS) was based on (i) body hair growth, (ii) breast development and (iii) menstruation.

For each item (except menstruation) four response categories indicate the extent of puberty from "not yet started" up to "seems complete". These were coded with values of 1 to 4 and summed up for each participant. According to these sum scores (and the stage of menstruation in girls) PCS was defined as Prepubertal, Early Pubertal, Midpubertal, Late Pubertal, Postpubertal. For the final binary analysis variable 'puberty' Midpubertal, Late Pubertal, and Postpubertal were considered as a positive puberty status.

Additionally, to gain more insight into possible effects of the age at puberty-onset in relation to the sex-shift of allergic diseases during puberty, we conducted a sensitivity analysis including the information of the time point of puberty-onset by using the age period 10-12 years for early and 13-16 years for late puberty-onset.

2.4 | Definition of possible confounders

Based on results from previous studies, we considered the following variables in the analyses as possible confounders: age (categorical (for all cohort-specific models except for MAS) or continuous (for models in the MAS cohort and in pooled data set)—depending on number of available follow-ups per cohort), history of parental allergies (yes = at least one parent with asthma and/or rhinitis diagnosis/no = two nonallergic parents) and maternal smoking during pregnancy (yes/no).[27,28]

2.5 | Statistical methods

For categorical variables, absolute and relative frequencies are presented. Results of all descriptive analyses are presented separately by cohort and pooled for all cohorts and sex. We pooled relative frequencies using random-effect meta-analyses.

We used generalized estimating equations (GEE) to estimate adjusted odds ratios (OR) and 95% confidence interval (CI) for the associations of the primary and secondary outcome variables with sex and puberty (and the interaction thereof) adjusting for the possible confounders described above, and age as the longitudinal time variable. The focus was on the interaction of puberty and sex as an indicator of sex-specific changes in outcome prevalence before vs after puberty onset. With GEE models, outcomes and exposure of the participants are analysed over time, taking the longitudinal design and thus the repeated measurements of one individual, which are not independent of each other, into account.

Initially, we pooled the harmonized cohort data sets to perform a one-stage Individual Participant Data (IPD) meta-analysis.[29] We used the GEE model described above on the combined data set of all cohorts with a birth cohort identifier variable included as an additional covariable in the model with participants nested in cohorts to account for the clustering in each cohort.

Additionally, as a comparative sensitivity analysis, we conducted a two-stage IPD meta-analysis, which consisted of the estimation of the adjusted odds ratios with the GEE model described above for each cohort separately as first stage and a subsequent random-effect meta-analyses with the inverse-variance method combining as second stage the adjusted effect estimates from all cohorts. Heterogeneity across the studies was assessed using the chi-squared Q-statistic and I^2.[30]

All our analyses are of explorative nature and we did not adjust for multiple testing. Missing values were not imputed. Thus, the number of included participants varied for more complex analyses including several variables and different number of missings per variable. We performed the meta-analyses in R version 3.1.2

(R Foundation for Statistical Computing) and all other analyses with SAS version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Description of cohorts

We included six birth cohorts with a total of 19 013 recruited participants: PIAMA (the Netherlands, 1996, n = 3963), BAMSE (Sweden, 1994, n = 4089), DARC (Denmark, 1998, n = 562) and three German birth cohorts (GINIplus, 1995, n = 5991; LISAplus, 1997, n = 3094; and MAS, 1990, n = 1314). We used data from birth to age 14-20 years (depending on the cohort). The number of observations used varied over follow-up time points due to dropouts and nonresponse. For analyses concerning the three GEE models for the primary outcomes, all necessary information (at least at one time point) was available for 14 533 participants.

3.2 | Puberty and exposure variables

In total, approximately 50% of the participants were female. Puberty started earlier in girls than in boys (eg, 62% vs 3% at age 11 in PIAMA, the Netherlands) with boys catching up in later teenage years (across the cohorts, except DARC), about 90%-99% of the participants had reached puberty according to our definition at the last included follow-up. Exposures such as self-reported parental allergies (ever) and maternal smoking differed slightly between the cohorts, but not considerably between boys and girls (Table 1).

3.3 | Prevalence of primary outcomes

3.3.1 | Current rhinitis only

Prevalence of current rhinitis only (ie, without coexisting asthma) varied between the cohorts. Among boys, it was generally higher than girls in earlier childhood, but this difference became smaller with increasing age (Figure 1; Table S1).

3.3.2 | Current asthma only

Prevalence of current asthma only differed slightly between the cohorts, with the highest prevalence in BAMSE across the follow-ups. At a younger age, more boys than girls had asthma but in teenage years these differences were smaller or even disappeared such as in GINIplus and BAMSE (Figure 2; Table S2).

3.3.3 | Allergic multimorbidity

Current allergic multimorbidity prevalence was higher among boys than girls especially in earlier childhood. These differences decreased as the participants grew older to smaller or even no differences between males and females (Figure 3; Table S3).

3.4 | Primary outcomes in relation to puberty

3.4.1 | Current rhinitis only

For current rhinitis only, the male predominance before puberty remained but was less pronounced after the onset of puberty. There was some degree of heterogeneity among the cohorts after puberty onset (I^2 = 39.6%) but not before puberty (Table 2). The pooled one-stage IPD meta-analysis also indicated this trend towards a female-male ratio decline (interaction sex*puberty onset P = .089) (Figure 4).

3.4.2 | Current asthma only

For current asthma only, we found a male predominance before puberty that decreased slightly after puberty onset. There was no heterogeneity among the cohorts (Table 2; Figure 4).

3.4.3 | Allergic multimorbidity

The strongest male predominance before puberty was found for allergic multimorbidity (OR: 0.55, 95%-CI 0.46-0.64). Furthermore, this outcome showed a clear shift towards a sex-balanced prevalence after puberty onset (0.89, 0.74-1.07), sex-puberty onset interaction term $P < .001$ (Figure 4). There was no considerable heterogeneity among the cohorts (Table 2).

3.5 | Sensitivity analyses: two-stage IPD meta-analyses

The additional two-stage IPD meta-analyses, which we performed as a sensitivity analyses, showed similar effect estimates for all three primary outcomes as the pooled one-stage IPD approach. The two-stage approach also allowed us to calculate I^2 for the assessment of potential heterogeneity between the cohorts. There was no considerable statistical heterogeneity for the primary outcomes apart for current rhinitis only with some moderate heterogeneity (Table 2).

3.6 | Sensitivity analyses: differentiating early and late puberty onset

Differentiating between early (age 10-12 years) and late puberty onset (age 13-16 years) did not change the effect estimates and the corresponding P-values for the interaction "pubertytime*sex" considerably compared to our primary analyses (Table S5).

3.7 | IgE- and non-IgE associated outcomes

3.7.1 | IgE- and non-IgE associated current rhinitis only and current asthma only

Prevalence estimates of IgE-associated current rhinitis only and asthma only were higher in male than in female participants before and to a lesser extent after puberty onset.

TABLE 1 Baseline characteristics and presence of puberty by age for each birth cohort and pooled

	PIAMA (n = 3963)		BAMSE (n = 4089)		GINIplus (n = 5991)		LISAplus (n = 3094)		DARC (n = 562)		MAS (n = 1314)		Total	
	Male n/N (%)	Female n/N (%)	Male n/N (%)	Female n/N (%)	Male n/N (%)	Female n/N (%)	Male n/N (%)	Female n/N (%)	Male n/N (%)	Female n/N (%)	Male n/N (%)	Female n/N (%)	Male %	Female %
Sex	2054/3963 (51.8%)	1909/3963 (48.2%)	2065/4089 (50.5%)	2024/4089 (49.5%)	2991/5830 (51.3%)	2839/5830 (49.7%)	1584/3094 (51.2%)	1510/3094 (48.8%)	285/562 (50.7%)	277/562 (49.3%)	684/1314 (52.1%)	630/1314 (48.0%)	51.3	48.8
Parental allergy	885/2025 (43.7%)	805/1889 (42.6%)	1001/2050 (48.8%)	976/2007 (48.6%)	1022/2340 (43.7%)	998/2214 (45.1%)	738/1470 (50.2%)	710/1384 (51.3%)	142/254 (55.9%)	143/255 (56.1%)	275/643 (42.8%)	300/601 (49.9%)	47.0	48.4
Maternal smoking during pregnancy	356/2037 (17.5%)	344/1889 (18.2%)	272/2065 (13.2%)	259/2023 (12.8%)	383/2474 (15.5%)	356/2327 (15.3%)	262/1524 (17.2%)	274/1450 (18.9%)	108/285 (37.9%)	75/277 (27.1%)	154/627 (24.6%)	154/584 (26.4%)	20.0	19.2
Puberty at age 10	-	-	-	-	63/1593 (3.9%)	170/1372 (12.4%)	31/853 (3.6%)	85/702 (12.1%)	-	-	0/394 (0%)	58/326 (17.8%)	1.9	13.6
Puberty at age 11	40/1316 (3.0%)	796/1295 (61.5%)	-	-	-	-	-	-	-	-	1/368 (0.3%)	147/299 (49.2%)	1.4	55.6
Puberty at age 12	-	-	424/1390 (30.5%)	1184/1353 (87.5%)	-	-	-	-	-	-	21/361 (5.8%)	261/346 (75.4%)	16.3	82.0
Puberty at age 13	-	-	-	-	-	-	-	-	-	-	117/373 (31.4%)	369/387 (95.4%)	31.4	95.4
Puberty at age 14	1092/1264 (86.4%)	1363/1366 (99.8%)	-	-	-	-	-	-	103/162 (63.6%)	199/212 (93.9%)	-	-	76.2	97.9
Puberty at age 15	-	-	-	-	1148/1268 (89.1%)	1316/1370 (96.1%)	683/741 (92.2%)	678/723 (93.8%)	-	-	289/315 (91.8%)	390/393 (99.2%)	90.8	96.6
Puberty at age 16	-	-	1231/1318 (93.4%)	1594/1623 (98.2%)	-	-	-	-	-	-	-	-	93.4	98.2

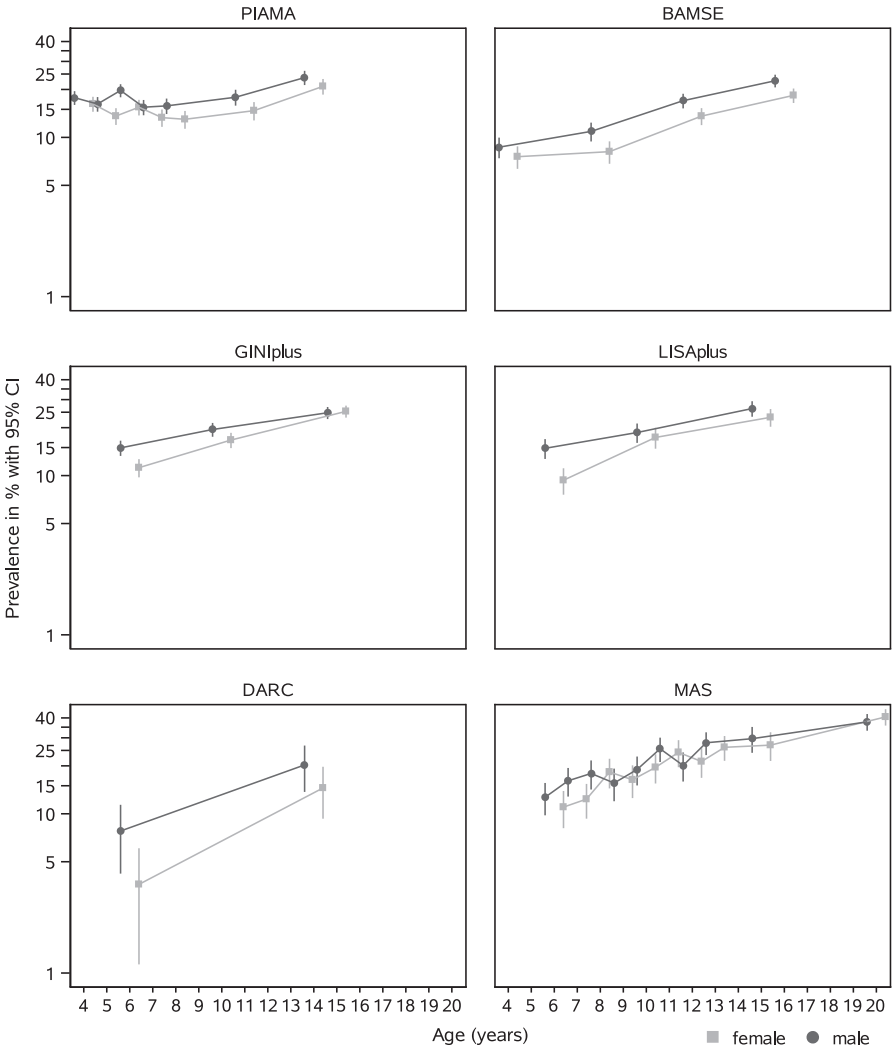

FIGURE 1 Sex-specific prevalence with 95% CI of current rhinitis only (on a logarithmic scale) in six European birth cohorts by age

In contrast, both non-IgE associated rhinitis only and asthma only showed sex-balanced prevalence estimates before puberty and a slight female predominance in the prevalence after puberty onset, corresponding sex-puberty interaction terms $P = .074$ and $P = .141$, respectively (Table 2).

3.7.2 | IgE- and non-IgE associated allergic multimorbidity

For IgE-associated allergic multimorbidity, we found a sex-shift from a strong male predominance before puberty towards a sex-balanced prevalence after puberty onset (sex-puberty interaction term $P < .001$). Similarly, non-IgE associated allergic multimorbidity showed also a sex-shift in the prevalence from a clear male predominance before puberty towards a sex-balanced occurrence of this phenotype after puberty onset (Table 2).

3.8 | Sensitivity analyses: allergic sensitization including IgE against aero- and food allergens

Including IgE against the common aero- and food allergens showed similar effect estimates for IgE- and non-IgE associated current rhinitis only, current asthma only and allergic multimorbidity compared to our primary definition of allergic sensitization status based only on common aero-allergens (Table S6).

4 | DISCUSSION

4.1 | Key results

Our individual participant data meta-analyses of six large European birth cohorts showed a strong male predominance before puberty for the prevalence of current allergic multimorbidity and to a lesser extent for current rhinitis and current asthma as single entities. After puberty onset, the sex-specific odds ratio shifted towards females in all phenotypes resulting in a rather sex-balanced prevalence for asthma only and particularly for allergic multimorbidity.

Considering allergic sensitization status, we found that for IgE-associated rhinitis only and asthma only, the clear male predominance decreased slightly, but remained significant after puberty onset, whereas for IgE-associated multimorbidity, we found a much stronger shift towards females with rather sex-balanced prevalence after puberty onset.

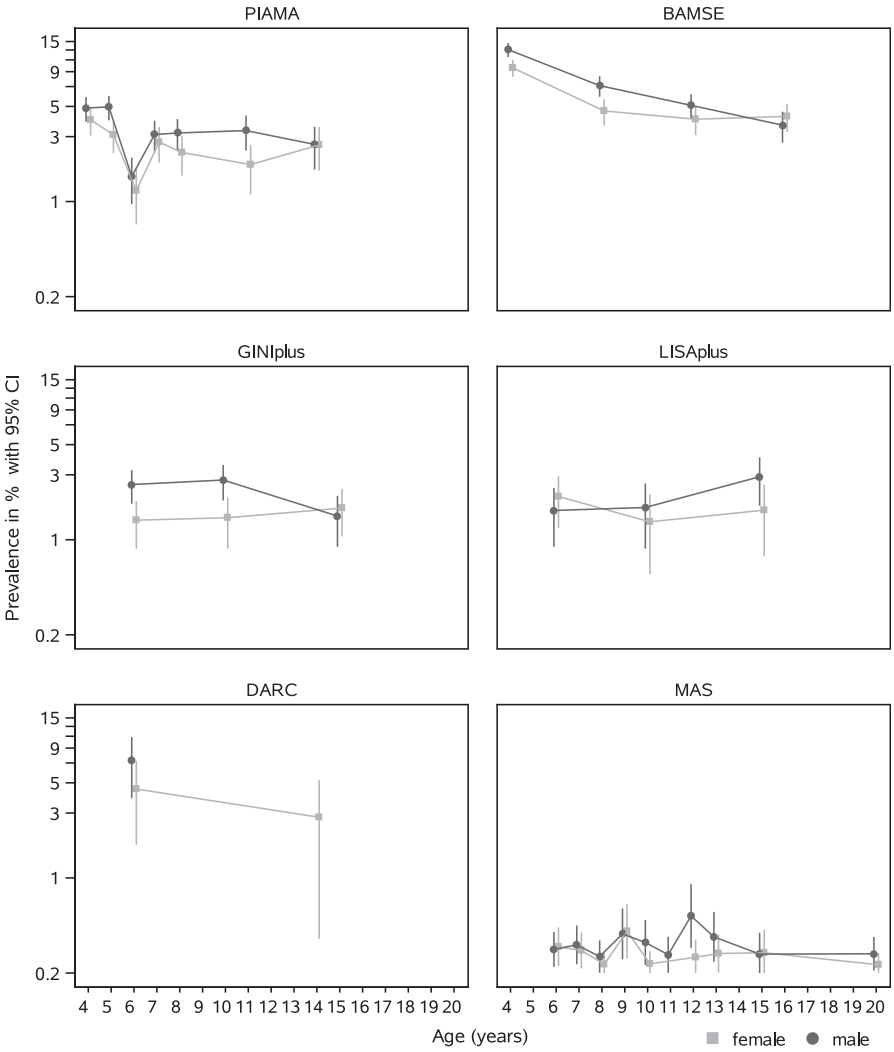

FIGURE 2 Sex-specific prevalence with 95% CI of current asthma only (on a logarithmic scale) in six European birth cohorts by age

The non-IgE associated (single and multimorbid) phenotypes showed a slight female predominance after puberty onset, which was strongest for non-IgE associated rhinitis.

4.2 | Strengths and limitations

Based on validated puberty assessments, this is the first longitudinal evaluation of birth cohort data assessing the sex-shift in prevalence at around puberty not only for rhinitis or asthma as single entities, but also for allergic multimorbidity. We combined prospectively collected data from six European birth cohorts from early childhood through adolescence up to age 20. For the IPD meta-analysis, we used pooled raw original data, which allowed us to define outcome and exposure variables, confounding variables and interactions consistently across the cohorts. Previous sex-shift evaluations had almost exclusively cross-sectional designs and used heterogeneous methods. This limited the comparability of sex-ratios before and after puberty onset between these studies, because the participants were not the same in the two groups (ie, before and after puberty). Due to the longitudinal character of the data in our study with homogeneous prospective assessments, comparability of sex-specific prevalence estimates before and after puberty onset can be considered more robust. Our findings gained external validity from the combination of several large cohorts showing similar results in different European regions and recruitment settings.

One limitation of (birth) cohort studies is that they are dynamic and prone to missing values during the course of repeated follow-up assessments as some participants, in particular teenagers, drop out or participate irregularly. This may cause selection bias and potentially limits the representativeness of the results.

Furthermore, at the time of the last follow-up included in our present analyses, some participants (PIAMA, the Netherlands, and DARC, Denmark) were just 14 years old and may not have reached puberty. The proportion of girls not in puberty was 0.2% (PIAMA) and 4.1% (DARC), which was comparable to the other cohorts with older participants at last follow-up, and for boys approximately 35% (DARC) and 15% (PIAMA). We cannot rule out a potential bias, especially if single cohorts will be analysed separately, but consider this risk of bias negligible in our large meta-analyses, where the absolute number of prepubertal participants at the last follow-up was comparatively small (eg, DARC represented <3% of all children recruited for

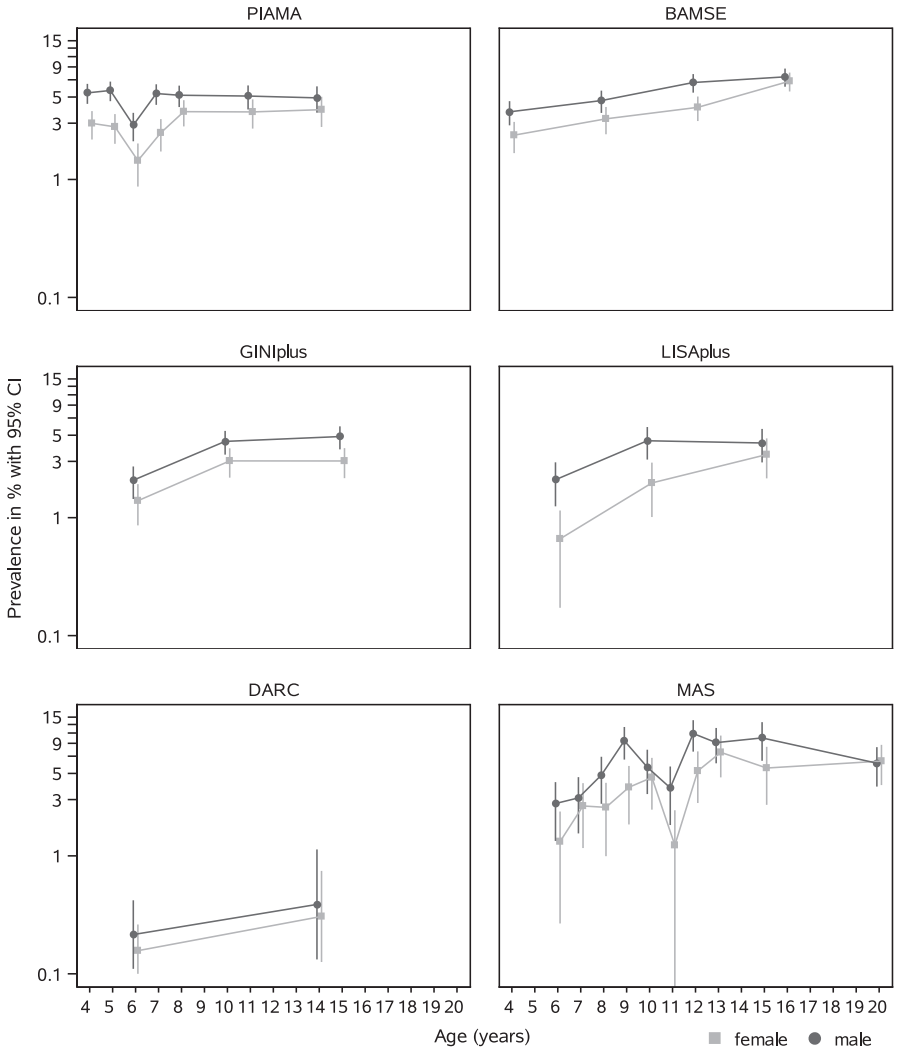

FIGURE 3 Sex-specific prevalence with 95% CI of current allergic multimorbidity (on a logarithmic scale) in six European birth cohorts by age

TABLE 2 Adjusted odds ratios[a] with 95% confidence intervals (CI) for sex effect (female vs male) before and after puberty for two-stage meta-analysis incl. assessment of heterogeneity among the cohorts using I^2

	Two-stage IPD meta-analysis Adjusted OR[a] (95%-CI) Heterogeneity I^2	
Outcome	**Before puberty onset**	**After puberty onset**
Current rhinitis only	0.78 (0.72-0.84) I^2 = 0%	0.90 (0.80-1.02) I^2 = 39.6%
Current asthma only	0.71 (0.62-0.82) I^2 = 0%	0.82 (0.64-1.06) I^2 = 4%
Current allergic multimorbidity	0.54 (0.46-0.65) I^2 = 11%	0.85 (0.71-1.03) I^2 = 0%
IgE-associated current rhinitis only (without asthma)	0.66 (0.52-0.84) I^2 = 54.9%	0.75 (0.66-0.86) I^2 = 22.1%
IgE-associated current asthma only (without rhinitis)	0.53[b] (0.40-0.70) I^2 = 0%	0.62[b] (0.42-0.91) I^2 = 2%
IgE-associated current allergic multimorbidity	0.52 (0.42-0.66) I^2 = 0%	0.84 (0.68-1.05) I^2 = 0%
Non-IgE associated current rhinitis only (without asthma)	0.94 (0.83-1.06) I^2= 0%	1.17 (1.02-1.34) I^2 = 0%
Non-IgE associated current asthma only (without rhinitis)	0.84[b] (0.69-1.03) I^2 = 0%	1.17[b] (0.81-1.72) I^2 = 0%
Non-IgE associated current allergic multimorbidity	0.73[b] (0.42-1.27) I^2 = 57.8%	0.97[b] (0.53-1.79) I^2 = 34.6%

[a]Adjusted for age, parental allergy and maternal smoking during pregnancy.
[b]Due to small prevalence in some cohorts not including all cohort estimators.

the 6 birth cohorts in total). We aimed to examine possible effects of the age at which puberty started by defining two main categories of early (age 10-12 years) and late onset (age 13-16 years) based on the assessment time points of the cohorts. We did not find a considerable impact of the timing of puberty with this approach. To analyse this aspect in more detail than in our sensitivity analysis was not

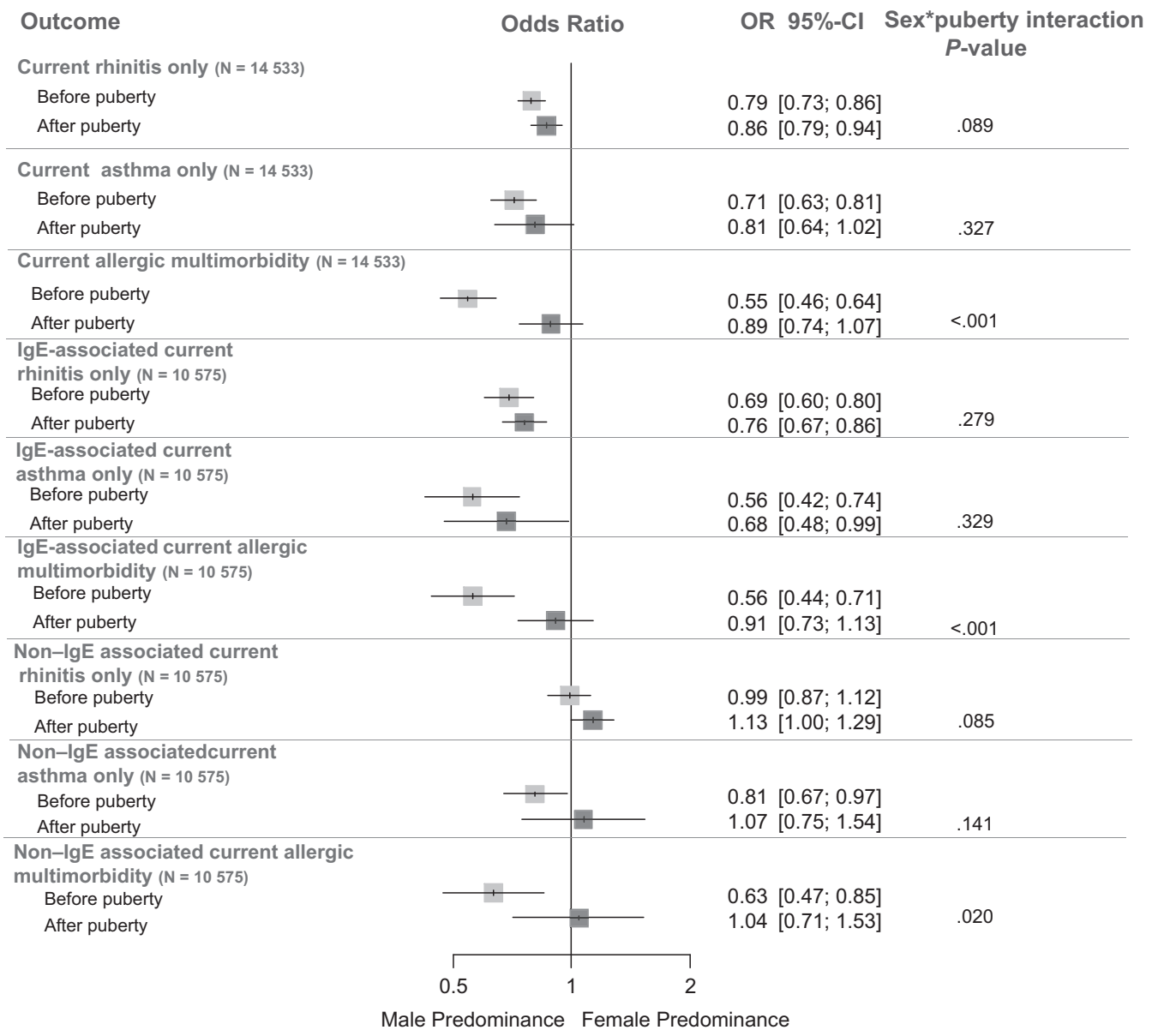

FIGURE 4 Odds Ratios from one-stage IPD meta-analysis of sex effect (female vs male) before and after puberty for all outcomes

possible because the cohorts differed in terms of the ages and follow-up intervals at which pubertal stage was assessed.

4.3 | Comparison to other studies

Pinart et al found a sex-switch for current (allergic) rhinitis prevalence from male to female predominance in their recent meta-analysis of published cross-sectional studies comparing childhood populations with adolescent and adulthood populations including mainly middle-aged participants. Participants of all birth cohorts included in our IPD meta-analyses except one had not reached adulthood yet. Therefore, we may have only found an indication towards a sex-shift but not a complete "sex-switch" in the prevalence of rhinitis as Pinart et al.'s analyses suggested. However, our findings point towards such an effect. Pinart et al.'s study differed further from ours as their meta-analyses focused on cross-sectional studies that mostly did not measure IgE sensitization, thus could not distinguish between IgE-associated and non-IgE associated rhinitis phenotypes.[31,32] Furthermore, the differentiation between rhinitis as a single or as part of a multimorbid phenotype was not made by Pinart et al[12] either.

In the Isle-of-Wight birth cohort study from the UK, which started in 1989, prevalence of sensitized and nonsensitized rhinitis in childhood and early adulthood showed a similar pattern to our findings. Concerning the differences in sensitization status of rhinitis patients, they showed a male predominance in rhinitis during early childhood as well as at 18 years of age only in subjects with rhinitis who were sensitized. For nonsensitized rhinitis, females in the UK cohort had a significantly higher prevalence at age 18 years.[33] Our results showed sex-balanced prevalence both before and after

puberty onset in teenage adolescents who were on average slightly younger. The theory that allergic sensitization might play a crucial role in the natural history of rhinitis can be reaffirmed considering sex differences.[34]

For asthma prevalence, several mostly cross-sectional evaluations showed a sex-switch from childhood to adolescence towards a female predominance.[5,7] We could not confirm a complete prevalence sex-shift for asthma prevalence, but a rather sex-balanced prevalence for asthma only after puberty. However, our statistical power was decreased when examining asthma without coexisting rhinitis and stratifying it by sensitized and nonsensitized subtypes. Therefore, we were not able to determine more precisely sex-specific prevalence differences in these strata. The TRAILS study from the Netherlands found a sex-shift between 11 and 16 years, but no association with pubertal stages as an explanation for the shift was found.[35] Other than in our study, they investigated asthma regardless of the presence of rhinitis which may explain the different findings.

Due to the common coexistence of asthma and rhinitis,[36] we aimed at evaluating sex-specific prevalence patterns in multimorbid patients to reduce the knowledge gap for these more severely affected patients. In particular, population-based research on sex-specific prevalence differences among multimorbid patients is scarce. The few earlier evaluations such as in the MAS[37] and BAMSE[38] cohorts showed an increasing prevalence of allergic multimorbidity with age. BAMSE found a male predominance in the prevalence of multimorbidity until the age of 12 that was confirmed by our analyses of multiple European cohorts. Regardless of allergic sensitization status, we found a stronger male predominance in the prevalence of allergic multimorbidity before puberty onset than for the single entities. In puberty, this clear sex-specific prevalence predominance decreased and shifted clearly towards a sex-balanced prevalence of multimorbidity after puberty onset. Based on the difference between prevalence in both individual morbidities and in multimorbidity, we hypothesize that this is not an additive effect but that due to the double burden different mechanisms may play a role.

4.4 | Potential mechanisms

Physiological changes during puberty such as endogenous[39] or exogenous sexual hormones (birth control pills)[40] have been proposed as potential determinants. Possible explanations include anatomical differences,[41] differences in the immune response profile such as increased IgE levels and enhanced cytokine responses in boys compared to girls in early childhood,[41,42] whereas in puberty and adulthood, female sex steroids are in general associated with enhanced immune responses and testosterone with dampening inflammatory responses.[43]

Sociocultural factors such as different symptom reporting behaviour between men and women[41] have been suggested as mechanisms behind the gender shift in allergic diseases. These are less of a concern in childhood as symptoms were parent reported but may play a role from school age on as teenagers fill out their own study questionnaires.

5 | CONCLUSIONS

In conclusion, we found the strongest male predominance before puberty for the prevalence of current allergic multimorbidity and also, but less pronounced, for current rhinitis and current asthma as single entities. With increasing age, we saw a "sex-shift" towards females resulting in a rather sex-balanced prevalence after puberty onset. This effect was much stronger in multimorbid children who had both current rhinitis and coexisting asthma than in those with rhinitis or asthma alone. We observed a larger prevalence shift towards females in nonsensitized than sensitized subjects.

Further cohort follow-up assessments are required to examine the hypothesized prevalence sex-switch to a female predominance regarding the different allergic phenotypes in adulthood.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

TKeller wrote the initial draft under supervision of SR and TKeil. TKeller developed the statistical analysis plan, conducted and interpreted the statistical analyses with supervision of SR. CH, TKeil, JMA and JB coordinated the harmonized follow-up assessment of all birth cohorts including the development of a common standardized questionnaire at age 14-20 and participated in the development of the statistical analysis plan. MS, AvB (GINIplus), JH, IL (LISAplus), UG, AW (PIAMA), EM, CA (BAMSE), SL, TKeil, UW (MAS), EE, ESC (DARC) coordinated the local follow-up assessments, and provided the newly as well as all the relevant previously collected birth cohort data. DM coordinated the harmonization of all previously collected data for the integration in a new common birth cohort database, provided harmonized data sets and participated in the coordination of the follow-up assessment. All authors read the different versions of the manuscript, provided comments, participated in the critical revision of the manuscript and the interpretation of the results, and approved the final version.

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SUPPORTING INFORMATION

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